

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY
DR. MICHAEL DEAN BERGER
FROM RECEIVING INVESTIGATIONAL NEW DRUGS

COMMISSIONER'S DECISION

In this proceeding of the Food and Drug Administration (FDA), the Center for Biologics Evaluation and Research (CBER), pursuant to 21 C.F.R. §16.26(a) and 21 C.F.R. §312.70, proposes to disqualify Dr. Michael Dean Berger from receiving investigational new drugs. CBER has moved to deny Dr. Berger's request for a hearing under 21 C.F.R. §16.26(a), and to disqualify him under 21 C.F.R. §312.70.

Based on my review of the parties' submissions, I find that there is no genuine and substantial issue of fact with regard to whether Dr. Berger repeatedly or deliberately violated 21 C.F.R. Part 312 regarding investigational new drugs. I am therefore granting the Center's motion to deny Dr. Berger's request for a hearing and I am disqualifying Dr. Berger from eligibility to receive test articles under 21 C.F.R. Part 312. As a result, Dr. Berger is no longer eligible to conduct any clinical investigation that supports an application for a research or marketing permit for FDA-regulated products, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or health claim, infant formulas, food and color additives, and tobacco products. Under the authority delegated to me by the Commissioner of Food and Drugs, I am issuing this Commissioner's Decision disqualifying Dr. Berger from eligibility to receive test articles under 21 C.F.R. Part 312 and

disqualifying Dr. Berger from eligibility to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

I. Background

Dr. Berger was the clinical investigator for (b) (4) research studies. The sponsor of the studies was Immunovative Clinical Research, Inc. FDA investigated the clinical study site and study records from April 27, 2010 until June 10, 2010. Based on the findings of that investigation, the Center initiated proceedings to disqualify Dr. Berger as a clinical investigator. The Center issued Dr. Berger a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) on September 26, 2011. Dr. Berger responded to the NIDPOE in writing. The Center accepted some of the explanations but not all with regard to the violations alleged. The remaining charges were related to A Phase I/II Study of an (b) (4)

(b) (4) As provided for in 21 C.F.R. § 312.70, the agency issued Dr. Berger a Notice of Opportunity for a Hearing on several remaining violations on December 18, 2012. Those violations included:

1. Failure to ensure that the investigation was conducted according to the investigational plan (21 C.F.R. §312.60);
2. Failure to report promptly to the IRB all changes in research activity and all unanticipated problems involving risk to human subjects or others, and made changes in the research without IRB approval (21 C.F.R. §312.66);
3. Failure to maintain adequate records of the disposition of the investigational drug, including dates, quantify, and use by subjects (21 C.F.R. §312.62(a)); and
4. Failure to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug, including case report forms and supporting data (21 C.F.R. §312.62(b)).

Dr. Berger requested a hearing. On November 13, 2013, CBER submitted its motion to deny Dr. Berger's request for a hearing and for disqualification.

II. Analysis

Under 21 C.F.R. 312.70, a clinical investigator will be disqualified from eligibility to receive test articles and to conduct certain clinical investigations, if after evaluating all available information, the Commissioner “determines that the investigator has repeatedly or deliberately failed to comply with the requirements of [Part 312],” Under the terms of the regulation, an investigator who either repeatedly or deliberately fails to comply with the investigational new drug regulations must be disqualified.

The Commissioner may deny a request for a hearing, in whole or in part, under 21 C.F.R. § 16.26(a), if the Commissioner or the FDA official to whom the authority is delegated to make the final decision on the matter determines that no genuine and substantial issue of fact has been raised by the material submitted. I have been delegated authority by the Commissioner to make the final decision on this matter.

The standard for denial of a hearing in 21 C.F.R. § 16.26 reflects the standard in federal court for summary judgment. *See John D. Copanos and Sons, Inc.*, 854 F.2d 510, 523 (D.C. Cir. 1988) (comparing standard under 21 C.F.R. § 314.200, which contains similar language, (“The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact”), to the standard for summary judgment in federal court). 53 Fed. Reg. 4613 (Feb. 17, 1988). Under Rule 56(c) of the Federal Rules of Civil Procedure, summary judgment is proper when there is no genuine issue as to any material fact and the moving party is entitled to judgment as a matter of law.

As is the case for summary judgment under Rule 56(c), the key criterion for determining whether denial of a hearing is appropriate is whether there are disputed facts that would affect the outcome of the proceeding. The moving party has the burden of showing that a rationale trier

of fact could not find for the nonmoving party and that there is no genuine issue for trial.”

Matsushita Electrical Indus. v. Zenith Radio Corp., 475 U.S. 574, 587 (1986). The opposing party may not rest on mere allegations that there are disputed issues of fact or denials of the moving party’s evidence. The opposing party bears the burden of producing “information ... to show that there exists a genuine and substantial issue of fact.” 53 Fed. Reg. 4613, 4614 (Feb. 17, 1988). If there are no genuine and substantial disputes of fact, denial of a hearing is appropriate.

FDA’s regulations provide for a clinical investigator to be disqualified if the investigator has “repeatedly” or “deliberately” failed to comply with the agency’s regulations governing clinical studies with investigational new drugs. CBER initiated this action against Dr. Berger under 21 C.F.R. § 312.70.¹ Under the regulation, a showing that a clinical investigator has *either* “repeatedly” *or* “deliberately” violated the relevant investigational new drug regulations is sufficient to disqualify the investigator. See Commissioner’s Decision, *In the Matter of James A. Halikas*, at 22-24 (2001). The meaning of “repeatedly” and “deliberately” has been considered in several Commissioner’s decisions disqualifying clinical investigators pursuant to 21 C.F.R. § 312.70. To establish “repeated” violations, the Center only needs show that a violation occurred more than once. Violations are repeated even if they occur within one study. See Commissioner’s Decision *In the Matter of William H. Ziering, M.D.* (2008) at 7; *Haikas* at 23.

The term “deliberately” has been interpreted to include indifference or a “willful” standard of intent. “[A] clinical investigator may be found to have acted ‘deliberately’ ... if he or she knowingly or willfully engaged in conduct that violated FDA’s regulations or if the investigator engaged in conduct that demonstrates a reckless disregard of FDA’s regulations.”

¹ CBER stated in its motion that it is pursuing disqualification of Dr. Berger under 21 C.F.R. § 312.70 as in effect prior to May 30, 2012. (CBER Motion, p. 1, Exhibit 1). FDA amended its regulations at section 312.70 in the Federal Register dated April 30, 2012 (see 77 Fed. Reg. 25353), effective date May 30, 2012. The amendment did not change the standard for disqualification but rather, among other things, changed the scope of the disqualification. This Commissioner’s decision applies the regulation currently in effect at 21 C.F.R. § 312.70.

See, Zierig at 8. This standard, then, does not require specific knowledge that one's behavior violates the law. A showing of a reckless disregard for what the regulations provide will suffice. *See Commissioner's Decision, In the Matter of Layne O. Gentry* (2008) at 20-21.

Although Dr. Berger requested a hearing in response to the NOOH, he did not submit any specific facts showing that there was a genuine and substantial issue of fact that warrants a hearing. In response to the NOOH issued by FDA, Dr. Berger responded that he wanted to use his NIDPOE response as his response to the NOOH (CBER Exhibit 9). Dr. Berger subsequently sent an undated letter to FDA in response to the NOOH. (CBER Exhibit 11). That letter included a copy of Dr. Berger's second NIDPOE Response Letter. This information, however, raised no genuine and substantial issues of fact regarding whether Dr. Berger violated FDA's clinical investigator regulations.

Based on Dr. Berger's responses which were included with the information presented in and attached to CBER's motion and all the other information before me, I find that, with respect to the charges alleged by CBER against Dr. Berger for violations of the regulations regarding investigational new drugs, there is no genuine and substantial issue of fact with regard to whether Dr. Berger repeatedly or deliberately violated 21 C.F.R. Part 312. I am therefore, granting CBER's motion to deny Dr. Berger's request for a hearing on the charges and because, these charges amount to "repeated" or "deliberate" violations of the regulation, I am also disqualifying Dr. Berger as a clinical investigator eligible to receive test articles under 21 C.F.R. Part 312 and disqualifying Dr. Berger from eligibility to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

I discuss each violation briefly below.

- 1. Dr Berger failed to ensure that the investigation was conducted according to the investigational plan [21 C.F.R. § 312.60].**

A. Dr. Berger failed to follow study protocol requirements concerning the dosing schedule and quantity of study drug to be administered to subjects.

CBER alleges that Dr. Berger failed to follow the investigational plan in three ways.

First, CBER charges that Dr. Berger failed to follow the study protocol requirement regarding the investigational drug dosing scheduling by failing to follow the study protocol requirement regarding the quantity of the study drug to be administered to subjects. The Center presents numerous examples of subjects that were dosed out of window, administered the drug by the incorrect route, and/or given numerous additional doses of the investigational drug. (See CBER Motion, Exhibits 12, p.91; Exhibits 13, 14, 15, 16, 17, 18; Exhibit 12, p. 93; Exhibits 20, 21, 22, 23, 24.) Dr. Berger admits that he did not follow the study protocol in these matters. He explained that he was given permission by the IRB to deviate from the approved protocol in this manner. However, the explanations provided by Dr. Berger do not raise any genuine and substantial issue as to whether he violated 21 C.F.R. § 312.60 which provides that the investigator is responsible for ensuring that the investigation is conducted according to the investigational plan. It was Dr. Berger's responsibility to ensure that the protocol requirements for the investigation drug dosing scheduling and the quantity of drug to be administered were followed. Although he alleges that the IRB gave him permission to deviate from the protocol (CBER Motion, Exhibit, pages 42-43; Exhibit 11, pages 69-70), he does not present any information that such approval was provided. He indicates he had no way of knowing or checking IRB internal procedures. Therefore, he claims he assumed that, if the IRB chairman said he could proceed to administer the drug, he assumed he had the right to assume the decision had undergone proper IRB procedures. (CBER Motion, Exhibit 11, p. 65.) However, Dr. Berger is not excused by his ignorance. It was his responsibility to know the IRB procedures and to

assure himself that he had the appropriate approval as required. Furthermore, Dr. Berger's allegations that he did not place patients at risk by his deviations (CBER motion, Exhibit, page 43; Exhibit 11, p. 70) or that use of adaptive trial design concepts to suggest changes in protocol dosing and scheduling would be useful in designing future studies (CBER motion, Exhibit 11, p. 67, item 10), also do not present any genuine and substantial of fact as to whether Dr. Berger violated 21 C.F.R. § 312.60 by failing to ensure that the investigation was conducted according to the investigational plan. Moreover, none of the reasons presented by Dr. Berger justify his violation of the FDA regulations which were promulgated to, among other things, protect the safety of human subjects during clinical studies. It is not for the individual investigator to determine whether he or she should deviate from the various requirements in the regulations.

B. Dr. Berger failed to follow the study's subject inclusion criteria.

CDER further asserts that Dr. Berger failed to ensure that the investigation was conducted according to the investigational plan because subjects were included in the study who failed to meet the inclusion criteria in the study protocol. CBER presented evidence for study subject (b) (6) (CBER motion; Exhibit 12, p. 95-96; Exhibit 28). The evidence demonstrated that study subject (b) (6) was included in the study even though the subject's (b) (4) (b) (4) laboratory values exceeded the inclusion values in the protocol. Dr. Berger agrees that the subject did not meet the inclusion values and that he admitted the subject who exceeded the inclusion/exclusion criteria to the study. (CBER Motion; Exhibit 6, p. 43; Exhibit 11, p. 70). He asserts, however, that the patient was being treated under a compassionate/emergency use approved by the IRB. Id. There is no evidence in the record to establish this assertion. All the evidence established that this patient was included in the study. Therefore, there is no genuine and substantial issue of

fact as to whether Dr. Berger violated section 312.60 of the regulations by failing to ensure that the investigation was conducted according to the investigational plan by including study subject (b) (6) in the clinical investigation.

C. Dr. Berger administered expired study drug to at least (b) (4) subjects in violation of the study protocol.

Finally, CBER alleges that Dr. Berger failed to ensure that the investigation was conducted under the investigational plan in violation of 21 C.F.R § 312.60 by administering the study drug to at least (b) (4) subjects after the drug had expired under the study protocol. As evidence, CBER cites to the “Chemistry, Manufacturing and Control” (CMC) document incorporated by reference into the study protocol. (CBER Motion, Exhibit 12, p. 84). The CMC document provides for the study drug to be administered within (b) (4) (CBER Motion, Exhibit 29, p. 177, section J.2.e.). CBER provided records from study subjects (b) (6) (b) (6) which indicate that the study drug was administered beyond the (b) (4) (b) (4) (CBER Motion, Exhibits 30, 31). Dr. Berger admits this violation of the study protocol. He provides various explanations for why it happened and that there was no safety issue. (CBER Motion, Exhibit 6, p. 44, Exhibit 11, p. 71). Dr. Berger, however, does not provide any information that raises a genuine and substantial issue of fact regarding whether he administered the study drug after the drug had expired under the study protocol and, therefore, failed to ensure that the investigation was conducted in accordance with the investigational plan in violation of 21 C.F.R § 312.60.

2. **Dr. Berger failed to report promptly to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and made changes in the research without IRB approval. [21 C.F.R. § 312.66].**

A. Dr. Berger failed to report to the IRB that (b)(4) lots of the study drug that were administered to subjects were subsequently found not to be sterile.

CBER asserts two violations of 21 C.F.R § 312.66 by Dr. Berger. Section 312.66 of the regulation provides that an investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others. CBER first alleges that Dr. Berger did not notify the IRB of administration to study subjects of lots of the study drug later found not to be sterile. CBER presents as evidence study records showing the (b)(4) lots of the study drug that were administered to subjects that were later found not to be sterile under the study's sterility testing procedures. (CBER Motion, Exhibit 32) However, there is no documentation that Dr. Berger ever advised the IRB of the problem.

Dr. Berger responded that he did not advise the IRB of the treatment of the study subjects with the non-sterile study drug. He said he notified the patients, determined there was no evidence of adverse events and that he thought the sponsor advised the IRB. (CBER Motion, Exhibits 33, p. 246, Exhibit 6, p. 45-46, Exhibit 11, p. 72-73). These actions however, do not raise a genuine and substantial issue of fact regarding whether Dr. Berger violated 21 C.F.R § 312.66 by failing to assure that he promptly reported to the IRB all unanticipated problems involving risk to human subjects.

B. Dr. Berger made changes in the research activity without IRB approval.

CBER further charges that Dr. Berger also violated section 312.66 of the regulations by failing to assure that he promptly reported to the IRB all changes in research activity in connection with his changes in the dosage scheduling and the quantity of study drug

administered to various patients. As evidence, CBER provides the study records for subjects (b) (6) (CBER Motion, Exhibit 34). However, Dr. Berger presents no evidence of IRB approval of the changes. He merely responds that he thought the changes were approved or that he was unfamiliar with the IRB procedures. (CBER Motion, Exhibit 11, p. 65) These responses do not raise any genuine and substantial issue of fact regarding whether Dr. Berger violated the regulation by failing to assure he did not make any changes in the research without IRB approval.

3. Dr. Berger failed to maintain adequate records of the disposition of the investigational drug, including dates, quantity, and use by subjects. [21 C.F.R. § 312.62(a)].

A. The study drug administration records for Subject (b) (6) and Subject (b) (6) contains inaccurate drug administration information.

CBER provides evidence that Subject (b) (6) received the study drug at (b) (4) (b) (4) (CBER Motion, Exhibit 35). CBER also presents as evidence the Administration Record for Subject (b) (6) which indicates the subject received a (b) (4). Likewise, the Treatment Summary record indicates Subject (b) (6) received a (b) (4). However, the (b) (4) (b) (4) record dated (b) (4) indicates that Subject (b) (6) received (b) (4) (b) (4) (CBER Motion, Exhibits 36, 37, 38).

Section 312.62(a) of the regulations provides that the investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. Dr. Berger's response to the inaccurate information regarding Subject (b) (6) and Subject (b) (6) was that the information was in error, he was unaware of omissions and inaccuracies, inaccuracies may have been result of recordkeeping errors by research nurse, and it was unfair for FDA to hold him responsible for errors discovered while the study was ongoing which could have been

corrected later after the sponsor's internal QA. (CBER Motion, Exhibit 5, p. 334-35, Exhibit 6, p. 47-48, Exhibit 11, p. 65, 74-75.). Although Dr. Berger has many reasons why the inaccuracies were not his responsibility, the regulation clearly makes him responsible. Dr. Berger's lack of regard for his responsibility to comply with the regulation indicated a deliberate violation of section 312.62(a). Dr. Berger does not raise any genuine and substantial issue of fact as to whether he violated section 312.62(a) by failing to maintain accurate records of the disposition of the investigational drug, including dates, quantity, and use by subjects.

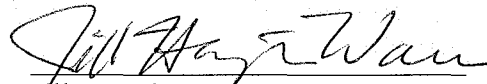
4. Dr. Berger failed to prepare and maintain adequate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigation drug, including case report forms and supporting data. [21 C.F.R. § 312.62(b)].

CBER charges that Dr. Berger violated FDA's regulations by keeping inaccurate records. CBER provided as evidence several forms that contained different information for the same dates, such as date subjects first received study drug, dates when subjects last received study drug, and date of subject's death, for the same study subjects. These discrepancies were noted for Subjects (b)(6) (CBER Motion, Exhibits 15, 17, 21, 39-57). Dr. Berger's response was not to deny the errors but to indicate that he would correct any errors that were pointed out to him, that a later internal sponsor QA would have caught these errors, and again that it was unfair for FDA to hold him responsible for error discovered while the study was ongoing which could have been corrected later after the sponsor's internal QA. (CBER Motion, Exhibit 11, p. 65, 75, Exhibit 6, p. 48.) Again, Dr. Berger's lack of regard for the accuracy of his study records and his responsibility to comply with section 312.62(a) indicated a deliberate violation of the regulation. He does not present any information that raises a genuine and substantial issue of material fact as to whether he violated section 312.62(a) of the regulations as charged by CBER.

III. Conclusion

Based on all the information available to FDA, I find that there is no genuine and substantial issue of fact regarding whether Dr. Berger repeatedly or deliberately violated FDA's clinical investigator regulations. Therefore, I am granting CBER's motion to deny Dr. Berger's request for a hearing on violations set out in the NOOH. I also find, after evaluating all available information, that Dr. Berger repeatedly or deliberately failed to comply with the requirements in 21 C.F.R. Part 312. Therefore, pursuant to 21 C.F.R. § 312.70, I am disqualifying Dr. Berger from eligibility to receive test articles under 21 C.F.R. Part 312. As a result of this determination, Dr. Berger is no longer eligible to conduct any clinical investigation that supports an application for a research or marketing permit for FDA-regulated products, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

Dr. Berger may seek to have his eligibility reinstated pursuant to 21 C.F.R. §312.70(f).



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